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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/821,710	04/08/2004	Michael Wayne Graham	546322000304	1697

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MORRISON & FOERSTER LLP
425 MARKET STREET
SAN FRANCISCO, CA 94105-2482

EXAMINER	
SULLIVAN, DANIEL M	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 09/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No. 10/821,710	Applicant(s) GRAHAM ET AL.	
	Examiner Daniel M. Sullivan	Art Unit 1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 25 August 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☒ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☒ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *See Continuation Sheet*. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: *44 and 47-61*.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See Continuation Sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

DANIEL M. SULLIVAN
PATENT EXAMINER

Continuation of 3. NOTE: The submission proposes to amend claim 44 such that the first RNA sequence is limited to 20-30 nucleotides in length. Applicant contends that support for this limitation is found in parent application 09/100,812 (now US Patent 6,537,099) at column 6, lines 25-30 of the issued patent. The cited passage reads, "Preferred structural gene components of the synthetic gene of the invention comprise at least about 20-30 nucleotides in length derived from a viral DNA polymerase, viral RNA polymerase, viral coat protein or visually-detectable gene.." (emphasis added). This passage clearly does not support an upper limit of 30 nucleotides as recited in the present claims. Furthermore, the passage is clearly referring to an element within a synthetic gene and does not teach an RNA sequence of 20-30 nucleotides. Therefore, the passage, viewed in context, does not support the subject matter embraced by claim 44 as amended..

Continuation of 11. does NOT place the application in condition for allowance because:

INFORMATION DISCLOSURE STATEMENT

In the previous Office Action it was stated that the information disclosure statement filed 29 April 2005 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

It was also stated, that the Examiner can find no PTO/SB/17 in the 29 April submission. This statement was an obvious typographical error, as the missing form is actually the PTO/SB/08 or PTO-1449, which would comprise (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. In response, Applicant has resubmitted the PTO/SB/17, which is insufficient in view of the fact that it does not contain any of the items indicated as missing. Applicant further states that the PTO/SB/17 was filed with the 29 April IDS, which is true. However, the submission does not contain a form comprising (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement as required.

OATH/DECLARATION

In response to the Examiner's assertion that, even if all of the unsupported subject matter were removed from the claims, the application, as filed, is a continuation-in-part and will remain a continuation-in-part throughout prosecution, Applicant contends that MPEP section 2163.06 indicates that objections and rejections to new matter should be withdrawn when the offending subject matter is removed. This argument has been fully considered but is not deemed persuasive. The section of the MPEP cited by Applicant concerns the addition of subject matter that was not part of the originally filed disclosure. In that case, the subject matter was not present in the application as filed. In contrast, the offending subject matter in the instant case was presented as part of the original disclosure. Although, as Applicant points out, the subject matter was added by preliminary amendment, the preliminary amendment was filed concurrently with the original application and, therefore, is part of the original disclosure. Consistent with this, the claims have not been rejected as containing new matter. Instead, the specification has been objected to for failing to provide antecedent basis for the subject matter in the claims and a newly signed oath has been required. Applicant requests that the Examiner show where the requirement for a new oath and designation of the Application as a continuation-in-part is supported in the MPEP. MPEP 602.05(a) states, "If the examiner determines that the continuation or divisional application contains new matter relative to the prior application, the examiner should so notify the applicant in the next Office action. The examiner should also (1) require a new oath or declaration along with the surcharge set forth in 37 CFR 1.16(e); and (2) indicate that the application should be redesignated as a continuation-in-part." The critical distinction between new subject matter filed as part of an original disclosure and new matter that is not part of an original disclosure is that any subject matter considered to be part of an original disclosure can be reintroduced and claimed during the prosecution of the instant application or in continuing applications that claim benefit of the instant application. Applicants must declare their belief that they are the original, first and sole (if only one inventor is listed below) or joint (if more than one inventor is listed below) inventors of the subject matter which is claimed and for which a patent is sought and, as the subject matter at issue was not present when the Declaration filed with the parent application was signed, a copy of that Declaration does not suffice in the instant case.

CLAIM REJECTIONS - 35 USC § 112, FIRST PARAGRAPH

Claims 44 and 47-61 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule comprising a first RNA sequence wherein said first RNA sequence is about 20-100 nucleotides in length and a second RNA sequence wherein said second RNA sequence is complementary to said first RNA sequence, wherein the first nucleic acid molecule is identical to a sequence complementary to a region of a target gene known at the time of filing to be capable of effecting post-transcriptional repression, delay or otherwise reduction of a target gene in a mammalian cell, does not reasonably provide enablement for the broad scope of any isolated nucleic acid molecule capable of post-transcriptionally repressing, delaying or otherwise reducing expression of a target gene in a mammalian cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In response to the prima facie case and arguments of record, Applicant first contends that recent developments in the field have indicated that the length of dsRNA is not the likely factor that is determinative in induction of the interferon response and as such claims to greater than 30 nucleotides would be enabled. However, Applicant does not provide any evidence or cite any evidence of record that would support this position. Therefore its validity cannot be evaluated. It is noted, however, that the enabled claim should be limited to comprising whatever element Applicant identifies as critical to avoiding interferon-induced non-specific RNA degradation in mammalian cells.

With regard to the Examiner's position that the disclosure is not enabling for the broad scope of any siRNA targeted to any given region of any given gene, Applicant contends that the unpredictability in obtaining RNAi is far less than that found in other biological systems. Applicant first cites section 2107.01(II) of the MPEP as indicating that an invention must be "wholly inoperative" to lack utility and that a small degree of utility is sufficient. However, this section of the MPEP has to do with the requirements for establishing that the utility asserted for an invention is "incredible", as evidenced by the title of the section cited by Applicant. In the instant case, no such assertion has been made.

Applicant further contends, "the ability to reduce expression of target genes of interest to a [sic] even to a small degree has utility as a research tool to evaluate whether the expression of the target gene is tightly regulated or if small changes in expression do not affect the overall activity." However, this asserted utility amounts to no more than testing the siRNA molecule to determine if a useful effect (i.e., an affect on the overall activity of the target gene) can be obtained. The Office does not view utilities that constitute carrying out further research to identify or reasonably confirm a "real world" context of use to be substantial utilities (See the Utility Examination Guidelines and Guidelines for Examination of Patent Applications under 35 U.S.C. §112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1092-1111, Friday, January 5, 2001).

Nevertheless, a utility rejection has not been made in the instant case because it is acknowledged that some embodiments within the scope of the claims have patentable utility (i.e., are capable of inducing a useful degree of sequence-specific degradation of an RNA transcript). It is important to recognize that 35 U.S.C. 112, first paragraph, addresses matters other than those related to the question of whether or not an invention lacks utility. These matters include whether the claims are fully supported by the disclosure (In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)), whether the applicant has provided an enabling disclosure of the claimed subject matter (In re Wright, 999 F.2d 1557, 1561-1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)), whether the applicant has provided an adequate written description of the invention and whether the applicant has disclosed the best mode of practicing the claimed invention (Chemcast Corp. v. Arco Indus. Corp., 913 F.2d 923, 927-928, 16 USPQ2d 1033, 1036-1037 (Fed. Cir. 1990)). See also Transco Products Inc. v. Performance Contracting Inc., 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994); Glaxo Inc. v. Novopharm Ltd. 52 F.3d 1043, 34 USPQ2d 1565 (Fed. Cir. 1995). The fact that an applicant has disclosed a specific utility for an invention and provided a credible basis supporting that specific utility does not provide a basis for concluding that the claims comply with all the requirements of 35 U.S.C. 112, first paragraph.

Next, Applicant contends that, in view of the level of utility asserted by Applicant to be sufficient, the invention is clearly enabled. Applicant first contends that the Deitz reference cited in the 8 February 2005 Office Action is not relevant to the claimed subject matter because siRNA works by a different mechanism than antisense RNA and siRNA is more effective. Applicant contends that Holen et al. supports enablement for the claims because, while Holen found a wide range of activities, most if not all of the constructs tested had some effect on expression and thereby met the required level of utility to support enablement. Applicant further argues that McManus et al. found that one in five constructs provided full silencing, which in most biological systems is a high rate of success.

These arguments have been fully considered but are not deemed persuasive. First, as discussed above, the minimal standard for "useful" gene suppression asserted by Applicant is not accepted as sufficient for patentable utility because using an siRNA to determine if the siRNA can affect the overall activity of a gene amounts to use testing of the siRNA. That is, as the "real world" utility of any siRNA stems from its ability to affect the overall activity of its target gene, the assertion that any siRNA can be used to determine if it has the capacity to affect the overall activity of its target gene does not support patentability of any given siRNA. Thus, an siRNA must be capable of altering the expression of the target gene to a degree sufficient to alter the physiological properties of a cell expressing that target gene in order to be considered as having "substantial" utility.

The teaching cited from Dietz et al. shows that suppression of gene expression by 80%-90% of the normal level is not typically sufficient to reduce the biological effect of the gene product (8 February Office Action at page 8). This finding is clearly applicable to a discussion of enablement for any method which purports to provide useful suppression of gene expression regardless of the means or mechanism of suppression. Dietz et al. teaches that even a very high degree of suppression is not typically sufficient to provide a biological effect. Therefore, effective RNA interference will require, in many cases, a very high degree of suppression which could not, at the time of filing, be predictably obtained using the methods of the instant invention.

Likewise, as pointed out in the 8 February Office Action, Holen et al. investigated the accessibility of the region surrounding the target site of the best siRNA identified therein and concludes, "[s]urprisingly enough, we found that despite the minimal sequence and position differences between these siRNAs, they displayed a wide range of activities (Fig. 2B)" (paragraph bridging pages 1758-1759). Thus, even siRNAs targeted within a narrow segment of the target gene can have dramatically different efficacy. With regard to McManus et al. it is not clear what Applicant is relying on for the teaching that 20% of siRNAs provide full silencing. However, it would seem that this teaching is limited to the particular CD4 and CD8-alpha genes targeted in that publication. Nevertheless, the teachings of McManus were cited as evidence that the probability of obtaining an effective siRNA varies from one target gene to the next. Therefore, obtaining a useful degree of sequence-specific degradation of an RNA transcript of a target gene using any given siRNA is unpredictable. Applicant's points out that generating a transgenic animal by cloning is only successful from 1-5% and the USPTO routinely allows claims to transgenic animals, which is true. However, it should be made clear that claims to transgenic animals typically allowed by the Office are limited to comprising modifications of specific genes. In contrast, the scope of the instant claims is analogous to claims covering all transgenic animals having a disruption in any gene, which the Office would not routinely allow.

With regard to working examples, Applicant acknowledges that the Examples are prophetic but asserts that they do work as asserted. However, Applicant provides no evidence to support this assertion. Furthermore, given the unpredictable nature of the art, even if there are some operative embodiments within the scope of the claims, which is in fact acknowledged by the Office, the claims are not generally enabled for the broad scope of what is presently claimed.

With regard to the quantity of experimentation, Applicant contends that McManus et al. teaches that typically only two constructs need to be tested to find a functional siRNA molecule that silences expression and asserts that even in the worst case scenario, one of skill in the art need only test five constructs to find a functional siRNA molecule that silences a gene. Applicant contends, "making five constructs is incredibly easy". This argument is not persuasive because even if one were to assume, arguendo, that one would only have to make five constructs to obtain silencing of any given gene (in fact the teachings of McManus et al., viewed as a whole, indicate that the number of constructs that must be tested to identify an siRNA capable of silencing any given gene is unpredictable), the claims encompass all nucleic acid molecules comprising a first RNA sequence greater than 20-100 nucleotides in length and identical to a sequence complementary to a region of any target gene and a second RNA sequence complementary to said first RNA sequence, wherein the nucleic acid molecule is capable of post-transcriptionally repressing, delaying or otherwise reducing expression of the target gene in any mammalian cell when the nucleic acid molecule is introduced into the mammalian cell.

Applicant's position ignores the scope of the claims, which is an important factor in determining whether a claim is enabled by the specification. The enabling specification must teach those skilled in the art to make and use the full scope of the claimed invention without undue experimentation. "Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.' In re Vaeck, 947 F.2d at 495, 20 USPQ2d at 1444; In re Wands, 858 F.2d at 736-37, 8 USPQ2d at 1404; In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (the first paragraph of section 112 requires that the scope of protection sought in a claim bear a reasonable correlation to the scope of enablement provided by the specification)." In re Wright (CAFC) 27 USPQ2d 1510 at 1513. Although, presence of inoperative embodiments within the scope of a claim does not necessarily render a claim nonenabled, the standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. "[I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. See, e.g., In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971)." Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). In the instant case, given the tremendous number of inoperative embodiments within the scope of the claims, the skilled artisan would not be able to practice the invention without undue experimentation.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole; therefore, the claims stand rejected under 35 USC §112, first paragraph, as lacking an enabling disclosure.

CLAIM REJECTIONS - 35 USC § 102

Claims 44 and 47-61 stand rejected under 35 U.S.C. 102(a) as being anticipated by Harborth et al. (publicly available 12 May 2003) Antisense Nucl. Acid Drug Devel. 13:83-105 for reasons of record and herein below.

Claims 44, 47, 54 and 56-61 stand rejected under 35 U.S.C. 102(b) as being anticipated by McManus et al. (2002) RNA 8:842-850 for reasons of record and herein below.

Claims 44, 47, 49-53, 56, 57, 60 and 61 stand rejected under 35 U.S.C. 102(b) as being anticipated by Elbashir et al. (2002) Methods 26:199-213 (made of record in the IDS filed 2 August 2004) for reasons of record and herein below.

Applicant's arguments with regard to claims 49-57 are predicated on entry of the amendment and, as the amendment has not been entered, are moot. With regard to the remaining claims, Applicant contends that the rejection of the claims is improper because the claims are entitled to benefit of the priority applications and therefore have an effective filing date prior to the publication date of the cited art. Applicant states that they have never encountered a 102 rejection based on an assertion that he claims are not entitled to a priority date due to lack of enablement and request that the Examiner show where his position is supported in the MPEP. The position is supported, inter alia, at MPEP 706.02(b), which states (emphasis added):

"A rejection based on 35 U.S.C. 102(b) can be overcome by...(C) Perfecting priority under 35 U.S.C. 120, within the time period set in 37 CFR 1.78(a) or filing a grantable petition under 37 CFR 1.78(a), by amending the specification of the application to contain a specific reference to a prior application or by filing an application data sheet under 37 CFR 1.76 which contains a specific reference to a prior application in accordance with 37 CFR 1.78(a), AND BY ESTABLISHING THAT THE PRIOR APPLICATION SATISFIES THE ENABLEMENT AND WRITTEN DESCRIPTION REQUIREMENTS OF 35 U.S.C. 112, first paragraph. See MPEP § 201.11 and § 706.02."

Thus, in order to obtain benefit of an earlier filing date and overcome an art rejection, the priority application must be enabling for the subject matter claimed. For reasons of record and herein above, the priority applications are no more enabling for the claimed subject matter than the instant application. Therefore, the claims are not entitled to benefit of the priority applications.

Applicant's arguments have been fully considered but are not deemed persuasive in view of the record as a whole; therefore, the claims stand rejected under 35 USC §102 as anticipated by the art.

CLAIM REJECTIONS - 35 USC § 112, SECOND PARAGRAPH

Claims 44, 47, 48 and 58-61 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. However, had the proposed amendment been entered, the rejection would be overcome.